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# Canadian Adverse Reaction Newsletter

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## Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

## Reporting Adverse Reactions

**Contact Health Canada or a Regional AR Centre free of charge**

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

**Form available at:**

www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

## Sterol and sterolin-containing products: hematologic adverse reactions

Although not approved by Health Canada, sterol and sterolin-containing products are used by some primarily for their presumed immune-enhancing properties. Plant sterols (phytosterols) are structurally related to cholesterol and perform the same functions in plant membranes as does cholesterol in animal membranes. The main phytosterols derived from the diet include }-sitosterol, campesterol and stigmasterol, all of which are unsaturated.[1] Sterolins are glucosides of sterols.[2] In humans, the absorption of phytosterols is low (5% or less of ingested sitosterol); however, people who have the rare inherited lipid storage condition known as phytosterolemia or sitosterolemia can absorb up to 63% of an ingested dose of sitosterol.[1]

Cholestasis and blood dyscrasias, including thrombocytopenia and hemolytic anemia, have been noted in adults and children receiving phytosterol-containing lipid emulsions with parenteral nutrition.[1,3,4] The thrombocytopenia associated with parenteral nutrition is similar to that observed in cases of phytosterolemia with increased peripheral destruction of platelets.[1,3] Reduced intake of such emulsions leads to decreased plasma phytosterol levels and subsequent alleviation of hepatic and platelet effects in some patients.[1,3]

A search of the Health Canada adverse reaction database revealed 4 reports in which sterol and sterolin-containing products were suspected of being associated with hematologic adverse reactions.

*Case 1:* After 2–3 weeks of taking "Moducare Sterinol" (1 capsule per day) a 22-year-old man experienced a life-threatening hemolytic anemia requiring admission to hospital and treatment with steroids, intravenous immune globulin therapy and a blood transfusion. At the time of the adverse reaction, the patient was not taking any concomitant medications; however, he had a history of severe idiopathic thrombocytopenic purpura (ITP) and splenectomy. Upon discontinuation of the product, the reaction slowly resolved.

*Case 2:* A 76-year-old man with a history of atrial fibrillation was taking Coumadin and had a stable international normalized ratio (INR) of 2.3–2.5. After an unknown interval of taking "Sterinol" (1 capsule per day), his INR fell to 1.6. Two weeks after discontinuing the Sterinol, his INR increased to 3.4. The patient began taking the Sterinol again, on a less frequent interval (1 capsule every 2 days), and his INR decreased to 2.0.

*Case 3:* A 75-year-old woman had been taking "Moducare" (1 capsule 3 times daily) for about 2 months when

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she experienced abdominal cramping and spotting. The first episode of spotting lasted 3 days, and the second episode lasted 7 days. The patient was taking concomitant drugs, including multiple antibacterial agents, an antihypertensive drug, a bone metabolism regulator (bisphosphonate), an $H_2$-receptor antagonist, a topical antineoplastic agent and inhalation aerosols.

*Case 4:* A 6-year-old girl was given "New Roots Herbal Sterols and Sterolins" once a day for about 2 years. The child presented with bruising, vaginal bleeding and thrombocytopenia. Her platelet count was 1 (normally 150–400) × $10^9$/L. Other abnormal hematological values were hemoglobin 101 (normally 110–157) g/L, hematocrit 0.29 (normally 0.34–0.46), erythrocyte count 3.7 (normally 3.8–5.6) × $10^{12}$/L, neutrophil count 8.6 (normally 0.8–7.2) × $10^9$/L and lymphocyte count 0.9 (normally 1.3–8.0) × $10^9$/L. The patient was given prednisone, and after discontinuation of the product she had fully recovered. She had no pre-existing medical conditions, nor was she receiving any concomitant medications. With respect to family history, it was noted that the patient's father had ITP at 4 years of age.

Health professionals are reminded to ask their patients to list the natural health products they are taking and to be vigilant of potential interactions.[5] Patients should be advised not to self-treat with products that claim to treat serious medical conditions.[6] Health Canada continues to monitor the safety profile of natural health products.

Scott Jordan, PhD; Jenna Griffiths, MSc, PhD; Karen Pilon, RN, Health Canada

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# Adverse reaction reporting — 2003

Health Canada received 9209 new domestic reports of suspected adverse reactions (ARs) in 2003. For the most part, ARs were reported by health professionals (pharmacists, physicians, nurses, dentists, coroners and others), either directly to Health Canada or indirectly through another source (Table 1). A further analysis of the total number of reports by reporter type (originator) is outlined in Table 2.

Of the AR reports received, 6414 (69.6%) were classified as serious. A serious AR is defined in the Food and Drugs Act and Regulations as "a noxious and unintended response to a drug which occurs at any dose and requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."

A steady increase in the reporting of ARs in Canada over the past 5 years has been noted, with 7.5% more reports in 2003 than in 2002 (Fig. 1).

Health Canada would like to thank all who have contributed to the program and encourages the continued support of post-marketing surveillance through AR reporting. ARs may be reported by using the toll-free telephone (866 234-2345) and fax (866 678-6789) lines.

Lynn Macdonald, BSP, Health Canada

**Table 1: Source of reports of adverse reactions (ARs) received by Health Canada in 2002 and 2003**

| | No. (and %) of reports received | | | |
|---|---|---|---|---|
| Source | 2002 | | 2003 | |
| Manufacturer | 5794 | (67.6) | 6125 | (66.5) |
| Regional AR centre | 2529 | (29.5) | 2671 | (29.0) |
| Other* | 243 | (2.8) | 413 | (4.5) |
| Total | 8566 | (100.0) | 9209 | (100.0) |

*Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

**Table 2: Number of AR reports by type of reporter (originator)**

| | No. (and %) of reports | | | |
|---|---|---|---|---|
| Reporter | 2002 | | 2003 | |
| Pharmacist | 2141 | (25.0) | 2369 | (25.7) |
| Physician | 2093 | (24.4) | 2176 | (23.6) |
| Health professional* | 1780 | (20.8) | 1974 | (21.4) |
| Consumer/ patient | 1581 | (18.5) | 1628 | (17.7) |
| Nurse | 421 | (4.9) | 689 | (7.5) |
| Other | 550 | (6.4) | 373 | (4.1) |
| Total | 8566 | (100.0) | 9209 | (100.0) |

*Type not specified in report

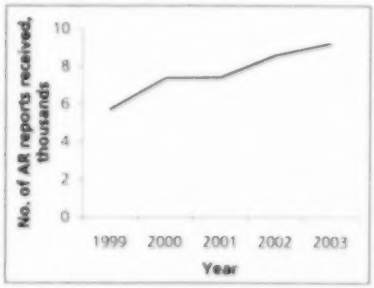


**Fig. 1: Number of adverse reaction reports received annually by Health Canada from 1999 to 2003.**

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

## Feasibility study of active surveillance of adverse reactions in children

In January 2004, the Marketed Health Products Directorate (MHPD) of Health Canada, in collaboration with the Canadian Paediatric Society and the Pharmaceutical Outcomes Programme of the Children's and Women's Health Centre of British Columbia, initiated a 3-year study to investigate the feasibility of using active surveillance methods to generate additional data on serious and life-threatening adverse reactions (ARs) in Canadian children under18 years of age.

Data will be collected through the Canadian Paediatric Surveillance Program (CPSP), an established active surveillance network that reaches over 2300 pediatricians and pediatric subspecialists monthly. These physicians provide health care to a geographically diverse pediatric population of over 6 million.

Health Canada continues to monitor and collect AR and medication incident reports, including those generated through the CPSP. All these data are also maintained in the national computerized database. This database is a major tool in the continuing assessment of marketed health products. The information from suspected AR and medication incident reports is analyzed to detect potential health product safety signals. A signal is considered to be the preliminary indication of a product-related issue. The identification of a signal is not by itself proof of an association between an AR and a health product; rather, it triggers the need to investigate a potential association further.

CPSP's study investigators are responsible for the review and analysis of data derived from the active surveillance study, both during and upon completion of data collection, which may result in the development of practice guidelines, published articles and presentations. MHPD of Health Canada is responsible for the coordination of consistency of post-marketing surveillance and the assessment of signals and safety trends concerning all marketed health products.

For more information on this study, visit the Canadian Paediatric Society's Web site (www.cps.ca/english/CPSP/Studies/drugreactions.htm).

## Case Presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

### Clopidogrel (Plavix): suspected association with hepatitis

Health Canada has received 2 case reports of hepatitis suspected to be associated with clopidogrel. An 84-year-old woman was prescribed clopidogrel (75 mg/d, orally) as adjunctive therapy to Aspirin to prevent further transient ischemic attacks. No other medications were reported. Eight weeks after starting the clopidogrel therapy, she presented with clinical and laboratory signs of acute mixed hepatocellular-cholestatic hepatitis. Serologic testing ruled out infectious causes, and results for autoantibodies were negative. There was no history of alcohol abuse and no history of toxic exposure. Further workup showed no evidence of biliary tract disease, hemochromatosis or other metabolic liver disease. Liver biopsy confirmed the finding of hepatotoxicity, and clopidogrel was discontinued. Complete resolution of symptoms and biochemical profile occurred over several weeks.[1]

The other case report described a flare-up of hepatitis with elevated liver enzyme levels in a 76-year-old woman who had been receiving clopidogrel for about 11 months. However, insufficient information was reported regarding the patient's concomitant medications or medical conditions, which limits our analysis of the report.

#### Reference

1. Barwa F, Lamoureux E, Friedman G. Clopidrogel-induced liver injury. *Can J Gastroenterol* 2003;17 (Suppl A):137.

## Public opinion survey on key issues pertaining to post-market surveillance of marketed health products in Canada

In 2003, Health Canada commissioned Decima Research to conduct a national survey of Canadians, including health care professionals, on their opinions on post-marketing surveillance of marketed health products (prescription drugs, nonprescription drugs and natural health products) available in Canada. Respondents provided important information on the effectiveness of Health Canada's methods used to communicate health product safety information. This feedback included perceptions of health product safety and health risks posed by adverse reactions (ARs); awareness, use of, familiarity and satisfaction with available sources of new health product safety information; views on mandatory AR reporting by health care professionals; and views on patient informed

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**Summary of health professional and consumer advisories posted from Nov. 18, 2003, to Feb. 9, 2004**

(advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

| Date | Product | Subject and type |
|---|---|---|
| Feb 9 | Tamiflu | Important safety information regarding Tamiflu (oseltamivir phosphate) and prescription in children less than 1 year of age — Hoffmann–La Roche Limited — health professional communication |
| Feb 3 | Newer anti-depressants | Health Canada advises Canadians under the age of 18 to consult physicians if they are being treated with newer anti-depressants — consumer information |
| Jan | Permax | Important safety information regarding the antiparkinson drug Permax (pergolide mesylate): sudden onset of sleep — Shire BioChem Inc. — health professional communication |
| Jan 27 & 22 | Fluticasone and ritonavir | Important safety information regarding a drug interaction between fluticasone propionate (Flonase / Flovent / Advair) and ritonavir (Norvir / Kaletra) — GlaxoSmithKline Inc. — consumer information and health professional communication |
| Jan 20 & 12 | Topamax | Topamax (topiramate) use is associated with metabolic acidosis — Janssen-Ortho Inc. — consumer information and health professional communication |
| Jan 15 & 13 | Eprex | Eprex (epoetin alfa) sterile solution: revised prescribing information for patients with chronic renal failure — Janssen-Ortho Inc. — consumer information and health professional communication |
| Dec 29 | IV tubing and monitor leads | Update: risk of strangulation of infants by IV tubing and monitor leads — notice to hospitals |
| Dec 23 | Kava | Health Canada reminds Canadians not to use products containing kava — consumer information |
| Dec 22 & Nov 28 | Pyrazinamide and rifampin | Serious liver injury with Tebrazid (pyrazinamide) or PMS-pyrazinamide and rifampin for the treatment of latent tuberculosis (TB) infection — ICN Canada Limited and Pharmascience Inc. — consumer information and health professional communication |
| Dec 18 & 4 | Beta-interferon | Hepatic injury associated with beta-interferon treatment for multiple sclerosis — Biogen Idec Canada Inc., Berlex Canada Inc. and Serono Canada Inc. — consumer information and health professional communication |
| Dec 16 | Blue food dye | Safety warning concerning the use of blue food dye in enteral feedings — notice to hospitals |
| Dec 12 | Comfrey | Health Canada advises consumers not to use the herb comfrey or health products that contain comfrey — consumer information |
| Nov 26 | Bell Magicc Bullet | Health Canada warns public not to use Bell Magicc Bullet — consumer information |
| Nov 17 | Sevorane AF | Important safety information regarding the use of Sevorane AF (sevoflurane) in conjunction with anesthesia machines — Abbott Laboratories Limited — health professional communication |
| Nov 11 | Clozapine | Important safety information regarding the dispensing of clozapine — letter to pharmacists |
| Nov 10 | Ventolin Diskus, Serevent Diskus, Flovent Diskus | Important safety information regarding the product recall notice for Ventolin Diskus / Flovent Diskus / Serevent Diskus inhalation devices — GlaxoSmithKline Inc. — letter to pharmacists and wholesalers |

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consent before AR reporting. These survey results will be used to evaluate the effectiveness of Health Canada sources of new drug safety information (e.g., Dear Health Care Professionals Letters, Public Advisories and the *Canadian Adverse Reaction Newsletter*) and will provide direction for improvements and baseline data for future evaluations. This report is available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_adr_reports_e.html.


# Canadian Adverse Reaction Newsletter

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